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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,244	12/27/2001	David Botstein	P2930R1C2	1015

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 06/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,244	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

1. Priority is granted to PCT 99/28634, published as WO 00/36102, since that application has the claimed protein sequence in figure 2.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 22-27 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of antibodies which bind to a protein termed PRO1800 in the specification.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the proteins. The cited utilities in the specification are that the protein is related to the Hep27 protein, which the specification states may be involved in some DNA synthesis related pathway. There is some evidence of overexpression in certain lung tumors (but not in others) at page 117. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the protein. No well established utilities for this specific

PRO1800 protein, antibody or nucleic acid are identified in either the specification or in the cited prior art.

Substantial utility

Given the absence of a well established utility, the next issue is whether substantial utilities are disclosed in the specification. Here, the evidence in the specification provided is that the protein is related by homology to the Hep 27 protein. This relationship lacks any of the hallmarks of utility. The homology does not imply that the proteins are similar in any function way, or that they are expressed in similar tissue types or under similar conditions. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner or any other specific feature which is disclosed as being associated with PRO1800. Without any further information, there is no expectation that the protein will have any properties in common with the Hep 27 protein. There is an abundance of evidence that very similar proteins can perform very different functions. For example, Rost et al (J. Mol. Biol. (2002) 318(2):595-608) notes regarding assignment of enzymatic activity based upon homology comparisons that "The results illustrated how difficult it is to assess the conservation of protein function and to guarantee error-free genome annotations, in general: sets with millions of pair comparisons might not suffice to arrive at statistically significant conclusions (abstract)." Thus, even high levels of homology do not necessarily correlate with actual protein function. In the current case, where not only is the function of PRO1800 not known, but no specific function has been definitively identified for the related Hep 27

protein itself, the expectation is even lower that there is any utility that can be derived based upon this association.

As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials). First, there is NO data in the specification showing association of PRO1800 with any disease state.

Second, the overexpression data does not provide a substantial utility for several reasons. First, there is no showing that the overexpression was statistically significant and correlated with any diagnostic utility. The absence of such a diagnostic utility is particularly striking since there is no evidence that the overexpression effect was statistically significant, that the effect was reproducible, or that the effect was anything other than a nonspecific effect due to the presence of an exogenous protein in the mixture. Finally, the claims at issue are drawn to antibodies. In the current case, there is no evidence that the protein is expressed in any particular tissue type. There is no evidence that the protein is overexpressed in cancerous cells, or that the protein has any utility whatsoever. As numerous references show, there is no necessary relationship between nucleic acid expression in a cell and protein expression. For example, Pennica et al (Proc. Natl. Acad. Sci. (1998) 95:14717-14722) shows that the Wisp-2 DNA was amplified by the RNA expression was reduced in tumors (see abstract). Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) states that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template. (see abstract)." So even if there

is a gene amplification, that would provide no utility whatsoever for the protein or antibody, since the gene amplification does not necessarily relate to the expression information of the protein and cognate antibody.

Third, the art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Similarly, Sawiris et al (Cancer Research (2002) 62:2923-2928) notes "One of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis (see page 2923, column 2)." Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on

the arrays or used at all. Therefore, such genes lack substantial utility as useful on gene expression arrays.

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for this protein and resultant nucleic acid. The protein has not been associated with any disease, any condition, any enzymatic activity or any other specific feature. The only association is that it has some homology to a protein, Hep 27, which is associated with DNA synthesis in some undefined way. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Here, there is no disclosure of any condition which can be diagnosed and hence, no specific utility.

Finally, with regard to the utility analysis, the current situation directly tracks Example 4 of the utility guidelines, where a protein of entirely unknown function was characterized as lacking utility.

Claim Rejections - 35 USC § 112 – Scope of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to antibodies which bind the PRO1800 protein. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass any antibody which binds to the PRO1800 protein and also include any antibody fragments which bind to the PRO1800 protein.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of polypeptides and antibodies. It would require significant study to identify the actual function of the PRO1800 protein, and identifying a use for this protein would be an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to protein function in the absence of reliable information regarding the protein activity. Even very similar proteins, as shown by homology, may have very different functions (see Rost et al (J. Mol. Biol. (2002) 318(2):595-608). In the current case, where no specific information is known regarding the function of the protein in actual biological organisms, it is entirely unpredictable what function and activity will be found for this protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the protein.

Further, the art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." This concept that genes whose expression does not change is irrelevant is not

limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Similarly, Sawiris et al (Cancer Research (2002) 62:2923-2928) notes "One of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis (see page 2923, column 2)." Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. Therefore, such genes lack substantial utility as useful on gene expression arrays.

Finally, the claims at issue are drawn to antibodies. In the current case, there is no evidence that the protein is expressed in any particular tissue type. There is no evidence that the protein is overexpressed in cancerous cells, or that the protein has any utility whatsoever. As numerous references show, there is no necessary relationship between nucleic acid expression in a cell and protein expression. For example, Pennica et al (Proc. Natl. Acad. Sci. (1998) 95:14717-14722) shows that the Wisp-2 DNA was amplified by the RNA expression was reduced in tumors (see abstract). Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) states that "Protein expression is not related to amplification of the abl gene but to variation in the level of

bcr-abl mRNA produced from a single Ph1 template. (see abstract)." So even if there is a gene amplification, that would provide no utility whatsoever for the antibody, since the gene amplification does not necessarily relate to the expression information of the antibody.

Working Examples

The specification has one working example in which the nucleic acid may be overexpressed in some tumor samples, but the working example was lacks sufficient information regarding internal controls to show that the protein was, in fact, overexpressed, that the nucleic acid was associated with any disease or that the results are anything other than spurious.

Guidance in the Specification.

The specification, while correlating PRO1800 with Hep 27, did not teach any actual function or use for PRO1800, nor, in fact, any use for Hep 27 itself.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art,

it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Declaration

6. The Declaration under 37 CFR 1.132 filed May 17, 2004 by Dr. Grimaldi is insufficient to overcome the rejection of the claims based upon 35 U.S.C. 101 or 112, first paragraph as set forth in the last Office action because:

The Declarant argues that for some genes, such as Her2/Neu or some chromosomal translocations such as T(5;14), the evidence supports the position that those genes are useful targets for cancer therapy.

This argument is entirely irrelevant to the current claims. Applicant is not claiming Her2/Neu or the T(5;14) translocation. Applicant is claiming an antibody to PRO1800. There is no evidence that this antibody has any use whatsoever. There is no evidence for the antibody of interest, an antibody to the gene product of PRO1800, as being cancer associated in any way. There is no known function associated with PRO1800. The association of PRO1800 as slightly homologous to another gene provides no information regarding the use or function of PRO1800.

Applicant then argues that the overexpression of genes results in immediate utility for an unknown gene. This is not consonant with the cited prior art. With regard to the issue of utility of irrelevant genes in microarrays, the prior art does not support the conclusion that such genes have utility. As is now noted in the rejections (to which the following paragraph was added in response to this declaration), the art supports the conclusion that many genes are irrelevant in gene microarray assays and completely

lack utility in these assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Similarly, Sawiris et al (Cancer Research (2002) 62:2923-2928) notes "One of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis (see page 2923, column 2)." Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. Therefore, such genes lack substantial utility as useful on gene expression arrays.

For these reasons and based upon these prior art references, the conclusion of the Declaration that PRO1800 has utility based on the ability to be used in microarray expression experiments is rebutted by three prior art references, each of which note that

many genes are irrelevant and simply represent noise. Therefore, the weight of the evidence supports a finding that there is no utility for the claimed invention.

Response to Arguments

7. Applicant's arguments filed May 17, 2004 have been fully considered but they are not persuasive.

As noted previously, Applicant argues that no prima facie case of lack of utility has been established. This is not correct. Applicant is referred to the rejection which provides specific reasoning on why the current applications lack utility.

Applicant then attempts to argue that the prior art does not say what is says. That is, Applicant argues that prior art which teaches that there is no necessary correlation between proteins and nucleic acids does not establish that fact in the current case. Applicant is misapplying the standard. Once the prima facie case that there is no utility is raised, Applicant is required to rebut that case with evidence. There is evidence in the rejection that there is no utility for the antibody and there is evidence in the rejection that there is no necessary relationship between nucleic acid expression in a cell and protein expression. For example, Pennica et al (Proc. Natl. Acad. Sci. (1998) 95:14717-14722) shows that the Wisp-2 DNA was amplified by the RNA expression was reduced in tumors (see abstract). Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) states that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template. (see abstract)."

So when Applicant argues this fact, Applicant fails to rebut the prima facie case since Attorney argument is not evidence. Further, the declarations of Dr. Grimaldi and Dr.s Goddard and Ashkenazi are not persuasive for the reasons given above and previously in response to these declarations. When applicant cites the declaration of Dr. Ashkenazi to support the use of genes on gene expression arrays, it is entirely irrelevant. In the current case, the antibodies are not genes and could not be used on such arrays. However, as noted in the response, even if they were genes, merely the existence of the gene does not provide utility for the claims on a microarray, since the art supports a conclusion that most genes are "irrelevant", to use the term of Ding et al or are simply "noise" to use the term of Sawiris. Adding something "irrelevant" or something that simply contributes "noise" does not provide utility.

Essentially, Applicant is attempting to capture control over antibodies to a protein with no known use, where the only relationship of any relevance to utility is based upon the nucleic acid. So there is no evidence that the protein or antibody themselves have any utility whatsoever. Applicant then provides three declarations which speculate that the proteins can be overexpressed and may be relevant or useful in some undefined future assay such as cancer diagnosis or treatment. This broad brush demonstrates the lack of utility. Treatment of cancer is not a trivial matter and it requires immense amounts of experimentation to identify compounds which will function in the productive treatment of cancer. In fact, the seminal utility case, Brenner v. Manson, dealt with treatment of cancer and asked the question of whether a chemical was useful "because the compound yielded belongs to a class of compounds now the subject of serious

scientific investigation." Brenner v. Manson, 148 USPQ 689, 695 (Sup. Ct. 1966. The Supreme Court answered "Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." There is no specific benefit in currently available form for the claimed antibody and it therefore lacks utility.

The same argument above applies to the enablement rejection, since there is no known use for the antibody, the antibody is not enabled for any use.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637